REMARKS

Claim Amendments

Claim 1 has also been amended to recite that "the modification is caused by an enzyme or enzyme activity that is increased at tumore cells or decreased at normal cells". Support for this amendment is found at page 23, lines 14-19 of the specification.

The limitations of Claim 7 have been incorporated into Claim 1.

Claims 23 has been amended so that the effector molecule and intracellular transport ligand are different. Support for this amendment is found on page 138, line 8 through page 140, whose teachings as a whole indicate that these two group are intended to be different structures. Specific note is made of liage 138, lines 13-16, which teaches that the drug itself need not possess the ability to be transported into the cell if a transport ligand is attached thereto.

Claims 1-3, 6, 8-23 and 27-29 have been amended to correct typographical errors and to put the claims in conditions for allowance. Detailed discussions of the Claim amendments and the support in the specification for these amended is provided below.

Claim Objections

Claims 1 and 2 are objected to because Claim 1 lacks a grammatical conjunction between sections III and IV and Claim 2 lacks a grammatical conjunction between sections V and VI. Claims 1 and 2 have been amended to add the phrase "and" to Claims 1 and 2.

Claim Rejections under 35 USC § 112 second paragraph

The Examiner asserts that Claims 1-22 and 27-29 are rejected under 35 USC § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner listed reasons (A) though (E) which are addressed in order below.

(A)

The Examiner asserts that Claim 1 is vague and indefinite because the association between E and T is undefined.

Applicant respectfully disagrees with the Examiner. The specification at page 26 line 20 line 1-26 (emphasis added) states:

> A preferred embodiment (embodiment ET7) of ET is comprised of the following groups:
>
> I. N1 targeting ligands, which can differ;
>
> II. N2 masked intracellular transport ligands which can differ;
>
> III. N3 triggers, which can differ, designated "detoxification triggers" wherein activation of the trigger decreases the pharmacological activity PA;
>
> IV. N4 effector agents which can differ;
>
> V. N5 triggers which can differ, wherein activation of the trigger increases the pharmacological activity PA;
>
> VI. N6 intracellular trapping ligands or masked intracellular trapping ligands, which can differ;
>
> and wherein:
>
> N1 = 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or about 10;
>
> N2 = 0, 1, 2, 3, 4, or about 4;
>
> N3 = 0, 1, 2, 3, 4, 5, or about 5;
>
> N4 = 1, 2, 3, 4, 5, or about 5;
>
> N5 = 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or about 10; and
>
> N6 = 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or about 10;
>
> and **wherein the components are covalently coupled directly or by one or more linkers**, and wherein the connectivity between groups can vary provided that the functionality of the different components remains intact and wherein the function of ligands is to bind to their respective receptors; the function of the triggers is to be activated and modulate drug activity, and the function of the effector agent is to evoke the pharmacological activity PA;

Linkers are defined in the specification page 4 lines 18-19:

LINKER – A chemical group that serves to attach targeting ligands, triggers and effectors or other chemical structures together.

Therefore the association between E and T is defined as being either a covalent bond directly between E and T or by covalent bonds between a linker and E and T. The association between E and T is clearly defined and withdrawal of the rejection is respectfully requested.

(B)

The Examiner asserts that Claim 1 is unclear because it is unclear what the pharmacological activity is in reference to.

Applicant respectfully disagrees with the Examiner. Page 6 lines 13-14 state:

PHARMACOLOGICAL ACTIVITY – A beneficial physical, chemical or biological response that is evoked by a drug or effector agent such as cytotoxicity or stimulation of the immune system or a diagnostic effect.

In light of the above definition the pharmacological activity referred to in Claim 1 refers to the activity of the drug ET and/or the activity or the effector E. Claim 1 has been amended to reflect that the pharmaceutical activity refers to the anticancer drug ET. Withdrawal of the rejection is respectfully requested.

(C)

The Examiner has objected to the "proviso" language in Claim 1 as no outcome of the provision is provided. Claim 1 has been amended to read "wherein T is not an antibody, or an analog of an antibody..."

(D)

The Examiner asserts that it is unclear how an antibody "analog" can be disclaimed because an antibody analog encompasses all binding agents of non-antibody origin. The Examiner appears to have concluded that an antibody analog is not required to have any structural similarity to an antibody and therefore the term "antibody analog" encompasses any molecule with binding specificity.

Applicant respectfully disagrees with the Examiner. Analog is defined in the specification page 4 lines 5-6:

> ANALOG – A compound or moiety possessing significantly structural similarity as to possess substantially the same function.

Therefore, the term "antibody analog" as used in Claim 1 refers to compounds or molecules with significant structural similarity to an antibody. Withdrawal of the rejection is respectfully requested.

(E)

The Examiner is objecting to the term "first and second" in Claim 1 as it lacks antecedent basis. Claim 1 has been amended to correct the lack of antecedent basis.

(F)

The Examiner is objecting to Claim 2 because it is unclear if the groups are referred to in the alternative or collectively. Claim 2 has been amended to clarify that the groups in Claim 2 are referred to collectively. The groups in Claim 2 have an additional limitation over Claim 1 of being restricted by the number of groups present in ET.

The values listed for each "N" are independently selected for each "N" and the claim has been amended to reflect this. For example, T may comprise 3 moieties from group I, in which case N1 is 3; 0 mmieties from group II, in which case N2 is 0; 3 moieties from group III, in which case N3 is 3; 3 moeities from group IV, in which case N4 is 3; 0 moeities from group V, in which case N5 is 0; 0 moeities from group VI, in which case N6 is 0. Applicant believes the claim is clear as written, and withdrawal of the rejection is respectfully requested.

(G)

The Examiner has objected to the term "about" in Claim 2. Claim 2 has been amended to remove the term "about". Applicant, however, would like to point out that this amendment is to clarify the claim. The claim scope is not narrowed as a result of this amendment.

(H) and (I)

The Examiner states that is unclear how the values in Claim 3 and 4 modify the claims from which they are dependent.

Claims 3 recites a more limited set of values for N1-N6. For example, N1 is permitted to be 1-10 in Claim 2, whereas N1 can only be 1-4 in Claim 3. Claim 4 has been cancelled, rendering the objection moot. Withdrawal is requested.

(J)

The Examiner states that it is unclear how Claim 5 further modifies Claim 4. Claim 5 has been canceled and the rejection is now moot.

(K)

The Examiner is objecting to the lack of antecedent basis for the term "compound" in Claims 3 and 4. Claims 3, 6-8, 10-14, 16-22, 28 and 29 have been amended to replace the term "compound" with "anticancer drug". Claim 4 has been cancelled.

(L)

The Examiner is objecting to the lack of antecedent basis for the term "biomolecule" in Claim 18. Claim 18 has been amended to replace the term "target biomolecule" with "target receptor".

(M)

The Examiner asserts that Claim 22 is vague and indefinite in the recitation of "an analog or derivative which bears amino acid sequence similarity to portions of a monoclonal antibody". Claim 22 has been amended to read:

> an analog ~~or derivative which bears amino acid sequence similarity to portions~~ of a monoclonal antibody; ~~or~~

Which is consistent with the language used in Claim 1. As discussed above in (D) an analog is defined in the specification page 4 lines 5-6:

> ANALOG – A compound or moiety possessing significantly structural similarity as to possess substantially the same function.

Therefore, the term "analog" as used in Claim 22 refers to compounds or molecules with significant structural similarity to a monoclonal antibody. Withdrawal of the rejection is respectfully requested.

(N)

As described throughout the specification E1T1 and E2T2 are embodiments of ET. As described above in (A) the association between E and T is either a covalent bond or a linker. E1 and T1 and E2 and T2 are embodiments of E and T and therefore the specification defines that they are bound either by a covalent bond directly between E1 and T1 or E2 and T2 or a covalent bonds between a linker and E1 and T1 or E2 and T2. The association between E1 and T1 or E2 and T2 is clearly defined and withdrawal of the rejection is respectfully requested.

Claim Rejections under 35 USC § 112 first paragraph

The Examiner asserts that Claims 12 and 27-28 are rejected under 35 USC 112 first paragraph, as failing to comply with the enablement requirement. Specifically, Claim 27 recites that "E1 and E2 are effector agents that exhibit synergistic toxicity" and the Examiner asserts that the "art recognizes the search for combinations of drugs exerting a synergistic effect requires a great deal of empirical testing". The term "synergistic" has been removed from Claim 27 by amendment. It is now believed that the rejection has been overcome and its withdrawal is requested.

Further, the Examiner states that the specification is non enabling for how to make "masked" cis-platin. However, neither E1T1 or E2T2 in Claim 27 comprise a "masked" cis-plantin which will regain toxic activity only after reaction with an activated metalloprotieinase as asserted by the Examiner. E1T1 and E2T2 in Claim 27 comprise only a targeting ligand and an effector agent. Withdrawal of the rejection is respectfully requested.

With respect to Claim 12, the Examiner alleges that the specification does not teach how to make an anticancer drug comprising a tumor selective targeting ligand which is not an antibody, and which consists of a targeting ligand and a trigger, wherein in vivo modification of said trigger increases the tumor killing activity and wherein in vivo modification of said trigger

decreases the tumor killing activity, wherein the effector agent is a drug that stimulates the immune system.

Claim 12 has been amended so that N3 is 0. As such, Claim 12 does not encompass a compound that comprises a trigger. As such, it is believed that the rejection has been overcome. Withdrjawal of the rejection is requested.

Claim Rejections under 35 USC § 102(b)

Claim 23 is rejected under 35 USC 102 (b) as being anticipated by Connors and Knox.

The Examiner states that Connors and Knox disclose the ADEPT system wherein the carboxyl peptidase A is delivered to the exterior of a cell via an antibody followed by the administration of methotrexate-alaine which is converted to methotrexate by reaction with the carboxypeptidase in the vicinity of the cells. The examiner states further that "methotrexate binds to the folic acid receptor which actively transports bound ligands into the cell". The examiner apparently interprets Claims 23 such that the effector group and the intracellular transport ligand are the same group. Applicant disagrees with this interpretation, but has amended Claim 23 to clarify that the effector group and the intracellular transport ligand are different groups. As such, the subject matter of Claim 23 is clearly novel. Withdrawal of the rejection is requested.

Claim Rejections under 35 USC § 103

The Examiner asserts that Claims 1-5, 10, 11, 13, 18, 21 and 22 are obvious over Glazier, in view of Brooks *et al.,* and Teti *et al.,* Fishman et al., and Connors and Knox.

Applicant respectfully disagrees with the Examiner.

Applicant's invention

The instant invention results, at least in part, from Applicant's appreciation that tumor cells have two or more features (hereinafter "Features"), typically proteins, that are overexpressed relative to normal cells. Tumor cells thus present a "pattern" of Features which can be used to design anti-cancer drug that "recognize" tumor cells and distinguish them from

normal cells (i.e., "Pattern Recognition"). These anti-cancer drugs comprise two or more different groups (hereinafter "Special Groups"). Each Special Group interacts with a different Feature to cause the drug to: selectively bind to the tumor cell; 2) to be selectively activated by the tumor cells; or 3) to be selectively incorporated into the tumor cells. Because each Special Group enhances the drug's selectivity for the tumor cells by interacting with a different Feature that distinguishes the tumor cells from normal cells, the selectivity of Applicant's anti-cancer drugs is potentially amplified compared with currently used anti-cancer drugs that do not recognize any Feature or recognize only one Feature on the tumor cells.

Rejejction Over Glazier in View of Brooks *et al.*, and Teti *et al.*, Fishman et al., and Connors and Knox

Glazier (U.S 5,659,061) teaches an anticancer phosphoramide type mustard derivative which is ***activated and released*** by a tumor associated protease. The Examiner appears to be taking the position that the phosphoramide type mustard derivative disclosed by Glazier is equivalent to the effector agent of Claim 1 and that the phosphoramide type mustard derivative also comprises a trigger which is modified by the tumor specific protease and results in activation of the phosphoramide type mustard derivative. However, Claim 1 requires in subsection a) that the claimed anticancer drug also comprise a "first tumor selective targeting ligand which selectively binds to a target receptor that is increased on the surface of a tumor cell or in the microenvironment of the tumor cell compared to that for vital normal cells." This feature is not present in the derivative disclosed by Glazier. Therefore, Glazier fails to teach or suggest an anti-cancer agent comprising ***both*** a targeting ligand ***and*** a trigger and consequently is deficient as a reference against Claim 1, even assuming *arguendo* that this interpretation is correct.

Connors and Knox do not cure this deficiency. The Examiner states that Connors and Knox disclose the ADEPT system wherein the carboxyl peptidase A is delivered to the exterior of a cell via an antibody followed by the administration of methotrexate-alaine which is converted to methotrexate by reaction with the carboxypeptidase in the vicinity of the cells. It appears that the Examiner is reasoning that methotrexate is the effector agent, the antibody is the targeting ligand of subsection a) and alaine is the trigger in section bII) that is acted on by

carboxypeptidase. Applicant respectfully disagrees with this interpretation. Specifically, Claim 1 requires that the targeting ligand of subsection a) and the trigger of subsection b) be part of the ***same*** drug, not administered as separate drugs as taught by Conners and Knox. As discussed above, Glazier also fails to teach an anti-cancer drug comprising ***both*** a targeting ligand ***and*** a trigger. For this reason alone, Conners and Knox fail to cure the deficiencies of Glazier. Secondly, alain, the purported trigger of subsection bII), is ***not*** acted on by an enzyme or enzyme activity that is increased at tumor cells; rather, alain is acted on by carboxypeptidase, which is ***exogenously administered as a second drug.*** It is noted that the "trigger" in Glazier is activated by tumor protease, i.e., ***a protein overexpressed by the tumor, not administered exogenously.*** Because of this dramatic difference in the mechanism of action of the drugs disclosed by Glazier and Conners and Knox, the skilled person would have no reason to combine the teachings of these references. Thirdly, subsection bII), requires that the trigger be acted on by an enzyme or enzyme activity that is increased at tumor cells. As noted, alain, the purported trigger of subsection bII), is ***not*** acted on by an enzyme or enzyme activity that is increased at tumor cells; rather, alain is acted on by carboxypeptidase, which is ***exogenously administered as a second drug.*** Finally, we note that the presence of ***both*** a targeting ligand ***and*** a trigger which is activated by overpressed proteins at or near the tumor is the feature which results in the potential amplification of tumor selectivity for the claimed anti-cancer drugs. The advantage of having both these drugs is completely unappreciated by both Glazier and Conners and Knox. Therefore, the claimed invention is non-obvious in view of this combination of references.

It is respectfully submitted that none of the other references cited in this rejection (Brooks, Teti and Fishman) cure the deficiencies of Glazier and Connors and Knox. None of these references teach or suggest putting a targeting ligand and trigger in the same anticancer drug. They also fail to appreciate the potential increase in selectivity relative to normal cells of anticancer drugs with a targeting ligand and trigger. Indeed, these references were cited by the examiner for other reasons. As such, it is believed that the claimed invention is non-obvious in view of this combination of cited references and withdrawal of the rejection is requested.

The teachings of Lauffer *et al.*, Denny *et al.*, Schlom, Liochev *et al.*, Sessler *et al.* (WO 90/10633), and Sessler *et al.* (U.S. Patent No. 5,580,543) were additionally applied in further

rejections under 35 U.S.C. 103. However, these references also do not remedy the deficiencies of Glazier, Brooks *et al.,* and Teti *et al.,* Fishman et al., and Connors and Knox. None of these references teach or suggest putting a targeting ligand and trigger in the same anticancer drug. They also fail to appreciate the potential increase in selectivity relative to normal cells of anticancer drugs with a targeting ligand and trigger. Indeed, these references were cited by the examiner for other reasons. As such, it is believed that the claimed invention is non-obvious in view of this combination of cited references and withdrawal of these rejections is requested.

Double Patenting

The Examiner asserts that Claims 1-5, 10, 13, 18, 21 and 22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 14 of US Patent No. 5,659,061 in view of Glazier, Brooks *et al.* and Teti *et al.* Fishman et al. and Connors and Knox.

Claim 14 is directed to an antineoplastic prodrug, which is converted to an active drug by a tumor associated protease.

As discussed above the teachings of Glazier, alone or in combination with Brooks *et al.* and Teti *et al.* Fishman et al. and Connors and Knox do not teach all the limitations of the present claims. As such, the instant claims would not be anticipated by or would not have been obvious over Claim 14 of Glazier alone or in light of Brooks *et al.* and Teti *et al.* Fishman et al. and Connors and Knox. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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